Strong hearts

Cardiac muscle cells respond to increased pressure and/or volume with growth. It is well known that exercise induces cardiac growth, but pathological factors, such as hypertension, induce this response as well. Now, Bruce Spiegelman and colleagues report that C/EBPβ regulates exercise-induced cardiac growth and that mice with a reduction in C/EBPβ are resistant to pathological hypertrophy (*Cell* 143, 1072–1083, 2010). Using a quantitative PCR–based method, they analyzed expression levels of all transcriptional components in exercised mice as well as in mice subjected to transaortic constriction (TAC). TAC mice showed equivalent levels of hypertrophy as exercised mice, although TAC mice displayed signs of pathological hypertrophy. The authors identified five genes expressed in cardiomyocytes that were regulated in exercised-induced or TAC-induced hypertrophy. Consistent with decreases seen in cardiomyocytes after exercise, reduction of *C/EBPβ* with short interfering RNA led to an increase in both cell size and number in rat cardiomyocytes *in vitro*. *C/EBPβ* heterozygotes showed a reduction of *C/EBPβ* mRNA similar to that seen in exercised mice. To assess a potential protective effect of loss of *C/EBPβ*, the authors performed TAC on *C/EBPβ* mice. These mice showed only a minor reduction in cardiomyocyte function after TAC, suggesting that *C/EBPβ* mice are resistant to pathological stress on the heart. ***PC***

NFKBIA deletions in glioblastoma

Glioblastomas typically show excessive activation of the EGFR pathway accompanied by deregulation of NF-κB, a transcription factor activated by EGFR signaling. Amplification of *EGFR* and activating mutations in *EGFR* are frequently observed in the classical subtype of glioblastoma but are less common in the nonclassical subtypes, suggesting alternate mechanisms for EGFR pathway deregulation in these tumors. Markus Bredel and colleagues (*N. Engl. J. Med.* published online, doi:10.1056/NEJMoa1006312, 22 December 2010) now report that deletions of *NFKBIA*, which encodes an inhibitor of NF-κB, are common in glioblastomas and are associated with unfavorable clinical outcomes. The authors analyzed 760 glioblastomas and detected heterozygous deletions of *NFKBIA* in more than 20% of cases. *NFKBIA* deletions occurred more frequently in nonclassical subtypes of glioblastoma and in tumors lacking *EGFR* amplification and were correlated with reduced survival. Notably, restoring NFKBIA expression in glioblastoma cell lines reduced their malignant properties and rendered the cells more sensitive to treatment with temozolomide, a drug commonly used in glioblastoma chemotherapy. These findings suggest that strategies to restore or stabilize NFKBIA expression might be an effective means of counteracting the oncogenic effects of deregulated EGFR signaling in glioblastoma and other cancers. *KV*

Epigenetic inheritance

Heritable epigenetic information is theorized to be environmentally modifiable, but evidence for transgenerational effects is limited. Now, Oliver Rando and colleagues report environmentally induced transgenerational reprogramming of metabolic gene expression in mice (*Cell* **143**, 1084–1096, 2010). The authors fed inbred males either control or low-protein diets from weaning to maturity, bred these mice with control females and did not expose the male mice to the pregnant mice or offspring. Because the male contribution to the offspring is limited to sperm by this experimental design, the effects of diet exposure must be epigenetically inherited. The authors profiled gene expression, microRNA expression and DNA methylation in the livers of the offspring. This analysis showed that genes involved in fat and cholesterol metabolism are upregulated in the offspring of males fed a low-protein diet, and that there is a corresponding decrease in the levels of cholesterol in the livers of these offspring. There was also an upregulation of genes and microRNAs associated with proliferation and DNA replication. They observed only subtle changes in DNA methylation profiles between the offspring of males fed control versus low-protein diets and did not find any substantial differences in DNA methylation profiles in sperm from males fed control versus low-protein diets, suggesting that other epigenetic mechanisms such as chromatin alteration may play a role. *EN*

Functional annotation of model genomes

The Model Organism ENCyclopedia Of DNA Elements (modENCODE) projects were developed to systematically annotate functional genomic elements across a range of model organism genomes and as a complement to the analysis in the human ENCODE project. Reports from the modENCODE projects for two key model organisms, *Drosophila* and *Caenorhabditis elegans*, are now reported in a collection of papers across several journals. The modENCODE Consortium reports an overview and integrative analysis of the *Drosophila* modENCODE datasets (*Science* **330**, 1787–1797, 2010). Their analysis includes over 700 large-scale genome-wide datasets profiling transcripts, chromatin, regulation and replication. They triple the proportion of the *Drosophila* genome that is annotated and bring the number of predicted genes to ~17,000. They develop a functional regulatory network, used to predict gene function, as well as stage-specific and cell-type–specific regulators. Mark Gerstein and colleagues report the integrative analysis of the *C. elegans* modENCODE datasets (*Science* **330**, 1175–1787, 2010). They report 237 genome-wide datasets surveying gene structure, transcriptome, developmental phases, regulation and chromatin organization. They report evidence for 1,650 new genes, bringing the total gene count to ~22,000, triple the number of reported RNA transcripts and increase the number of non-coding RNAs by 20-fold. *OB*

Pediatric medulloblastoma landscape

To provide insights into the pathogenesis of pediatric medulloblastoma, Victor Velculescu and colleagues sequenced all protein-coding and microRNA genes and analyzed copy number alterations in 22 medulloblastomas (*Science* published online, doi:10.1126/science.1198056, 16 December 2010). A key finding was that each tumor has five to ten times fewer mutations compared to adult solid tumors that have been previously sequenced. On average, the number of non-silent somatic mutations in each medulloblastoma was 8.3, compared to 36–101 of these mutations seen in four other types of adult tumors. In addition, the proportion of nonsense mutations in medulloblastomas was over two times higher than expected. On average, 9.8% of the mutations in medulloblastomas were nonsense mutations, compared to 5.2–5.8% observed in four different adult tumor types. The authors also analyzed a subset of mutated genes in another set of 66 primary medulloblastomas. Notably, 20% of these tumors had a mutation in genes involved in chromatin remodeling and transcriptional regulation. They observed inactivating mutations in the histone-lysine N-methyltransferases MLL2 and MLL3 in 16% of tumors. These data provide an in-depth view of medulloblastomas and identify notable differences between pediatric medulloblastoma and other types of adult tumors. ***PC***

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